

Cognitive rehabilitation for attention and memory in people with multiple sclerosis: a randomized controlled trial (CRAMMS)

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Abstract

Objective: To assess the clinical and cost-effectiveness of cognitive rehabilitation for attention and memory problems in people with multiple sclerosis.

Design: Multicentre, pragmatic, randomized controlled trial.

Setting: Community

Participants: People with multiple sclerosis aged 18–69 years, who reported cognitive problems in daily life and had cognitive problems on standardized assessment.

Interventions: A group cognitive rehabilitation programme delivered in 10 weekly sessions in comparison with usual care.

Main measures: The primary outcome was the Multiple Sclerosis Impact Scale Psychological subscale at 12 months after randomization. Secondary outcomes included measures of everyday memory problems, mood, fatigue, cognitive abilities and employment at 6 and 12 months after randomization.

Results: In all, 245 participants were allocated to cognitive rehabilitation and 204 to usual care. Mean Multiple Sclerosis Impact Scale Psychological at 12 months was 22.2 (SD=6.1) for cognitive rehabilitation

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and 23.4 (SD = 6.0) for usual care group; adjusted difference -0.6 , 95% confidence interval (CI) = -1.5 to 0.3 , $P = 0.20$. No differences were observed in cognitive abilities, fatigue or employment. There were small differences in favour of cognitive rehabilitation for the Multiple Sclerosis Impact Scale Psychological at 6 months and everyday memory and mood at 6 and 12 months. There was no evidence of an effect on costs ($-\pounds 808$; 95% CI = $-\pounds 2248$ to $\pounds 632$) or on quality-adjusted life year gain (0.00; 95% CI = -0.01 to 0.02).

Conclusion: This rehabilitation programme had no long-term benefits on the impact of multiple sclerosis on quality of life, but there was some evidence of an effect on everyday memory problems and mood.

Keywords

Multiple sclerosis, cognitive impairment, memory, cognitive rehabilitation, cost-effectiveness

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Introduction

Up to 70% of people with multiple sclerosis experience cognitive problems, which negatively impact on function and quality of life.¹ Cognitive rehabilitation is a structured set of therapeutic activities to retrain cognitive skills or to improve people's ability to cope with cognitive deficits in daily life. However, the evidence for the effectiveness of cognitive rehabilitation is weak. Several systematic reviews have found some positive effects of cognitive rehabilitation in people with multiple sclerosis, but these are based on poor quality randomized controlled trials (RCTs) with several methodological shortcomings, with review authors suggesting the level of evidence is 'low'.²⁻⁴ No trial has evaluated the cost-effectiveness of cognitive rehabilitation. Therefore, the reviews have concluded that more high-quality trials are needed before firm conclusions can be reached.²⁻⁴

Although there is some support for the effectiveness of computerized cognitive rehabilitation to retrain cognitive skills in people with multiple sclerosis,⁴ these studies have rarely included any long-term follow-up to assess whether the observed benefits persisted or generalized to daily life. There is less evidence for cognitive rehabilitation to teach people skills to cope with the cognitive impairment and provide aids to enable them to compensate for the loss of cognitive abilities. The ReMIND trial⁵ ($n = 72$) evaluated the effectiveness of two types of group memory rehabilitation programme in neurological patients with memory problems, many of whom had multiple sclerosis ($n = 39$). The memory

rehabilitation programmes focussed either on restitution strategies (e.g. drill and practice exercises and teaching people to break down memory tasks into constituent parts) or compensation strategies (e.g. using external memory aids). The data from the study indicated that the interventions were worthy of further evaluation. Carr et al.⁶ ($n = 48$) combined the restitution and compensation strategies from the ReMIND trial and compared this with usual care for patients with multiple sclerosis. The results showed a beneficial effect on mood, favouring cognitive rehabilitation.

Therefore, the present trial was designed to assess the clinical and cost-effectiveness of this cognitive rehabilitation programme for people with multiple sclerosis.

This article reports the main outcomes with further details available elsewhere.⁷

Methods

This was a pragmatic, multicentre, observer-blinded RCT comparing a cognitive rehabilitation programme (intervention) in addition to usual care, with usual care alone (control). The trial was conducted in five sites in England. Participants were identified through United Kingdom National Health Service hospitals, charities (e.g. MS Society) and the United Kingdom MS Register. Ethical approval was granted by West Midlands, South Birmingham Committee (Ref. 14/WM/1083), and the protocol was published⁸ and the trial was prospectively registered (ISRCTN09697576/14/08/2014). This work was funded by the National Institute for Health

Research Health Technology Assessment programme (project number 12/190/05).

Participants were recruited between 13 March 2015 and 23 March 2017. People with multiple sclerosis were eligible if they were

- Aged 18–69 years.
- Diagnosed with relapsing–remitting or progressive multiple sclerosis.
- Diagnosed at least three months prior to the screening assessment.
- Reported having cognitive problems defined as >27 on the patient version of the Multiple Sclerosis Neuropsychological Screening Questionnaire.⁹
- Impaired on at least one of the Brief Repeatable Battery of Neuropsychological tests,¹⁰ defined as performance >1 standard deviation (SD) below the mean of healthy controls, corrected for age and education.¹¹
- Able to attend group sessions.
- Able to speak English sufficiently to complete the cognitive assessments.
- Gave written informed consent.

Potential participants were excluded if they

- Had vision or hearing problems, such that they were unable to complete the cognitive assessments.
- Had concurrent severe medical or psychiatric conditions, which prevented them from engaging in treatment.
- Were involved in other psychological intervention trials.

Demographic and clinical information were recorded. The Brief Repeatable Battery of Neuropsychological tests¹⁰ and Multiple Sclerosis Neuropsychological Screening Questionnaire⁹ were administered by an Assistant Psychologist to check that participants met the inclusion criteria. The postal version of the Guy's Neurological Disability Scale¹² was administered to record the level of disability.

Eligible participants were then given the following questionnaires to complete in their own time:

- Multiple Sclerosis Impact scale¹³ version 2, to assess the impact of multiple sclerosis on quality of life.
- General Health Questionnaire 30,¹⁴ to detect psychological distress.
- Everyday Memory Questionnaire – participant version,¹⁵ to assess the frequency of cognitive problems in daily life.
- Fatigue Severity Scale¹⁶ five-item Rasch-analysed version, to assess fatigue.

Participants were asked to nominate a relative or friend to complete the Everyday Memory Questionnaire – relative version.¹⁵

At a subsequent visit, the Assistant Psychologist administered the following assessments:

- Doors and People,¹⁷ an objective measure of memory function.
- Trail Making Test,¹⁸ to assess attention and executive abilities.
- European Quality-of-Life five-level version (EQ-5D-5L),¹⁹ a generic health-related quality-of-life measure to calculate Quality-Adjusted Life Year scores (QALYs).
- Use of Health and Social Services questionnaire to assess healthcare utilization and services provided by charities.

The Assistant Psychologist checked participants' availability to attend groups, should they be randomized to receive the intervention, and checked their preference to receive the outcome questionnaires by post or on-line.

Groups of 9–11 participants who could potentially attend for treatment at the same time and venue were individually randomized to either intervention or usual care on a 6:5 ratio. Allocation was stratified by recruitment site and minimized by multiple sclerosis type (relapsing–remitting or progressive) and gender. The allocation algorithm was held on a secure server and the Assistant Psychologists at each site used a remote, Internet-based randomization system to obtain treatment allocations for each participant. Assistant psychologists and participants were aware of the group allocation.

Usual care comprised general advice from multiple sclerosis nurse specialists and occupational therapists on how to manage any cognitive difficulties. All participants were notified of information available on the webpages of multiple sclerosis charities, which include suggestions for coping with cognitive problems. All other clinical services, and support from specialist charities, were available as part of usual care. The usual care that participants received was recorded on the Use of Health and Social Services questionnaire.

Cognitive rehabilitation was provided by an Assistant Psychologist to groups of four to six participants, who met approximately weekly for 10 sessions. The content of sessions was defined in a treatment manual (see supplementary material), which was developed in a previous study.⁶ The intervention included restitution strategies to retrain attention and memory functions and strategies to improve encoding and retrieval. Compensation strategies taught included the use of internal mnemonics (such as chunking) and external devices (such as diaries and mobile phones) and ways of coping with attention and memory problems. Attendance was recorded. If participants missed a session, they could attend early for the following session to catch up on the content they had missed. Homework assignments facilitated individualisation of care and generalization of cognitive strategies to daily life.

Outcomes assessed at 6 and 12 months after randomization included the Multiple Sclerosis Impact Scale, Everyday Memory Questionnaire – participant version, General Health Questionnaire 30, Fatigue Severity Scale, Brief Repeatable Battery of Neuropsychological tests, Doors and People, Trail Making, EQ-5D-5L, Use of Health and Social Services questionnaire and employment status. The Guys Neurological Disability Scale and number of relapses in the previous six months were also recorded. In addition, the participants' nominated relative or friend completed the Everyday Memory Questionnaire – relative version and Modified Carer Strain Index.²⁰

Questionnaires were returned by post or completed on-line. Research Assistants, blind to treatment allocation, conducted outcome visits to complete cognitive tests and the Use of Health and Social Services questionnaire.

The Multiple Sclerosis Impact Scale Psychological subscale at the 12-month follow-up was the primary outcome. A difference of 3–3.5 points on the Multiple Sclerosis Impact Scale Psychological subscale was considered clinically meaningful. Based on the Multiple Sclerosis Impact Scale Psychological subscale, 143 participants per group were required to detect a difference of 3 points, assuming an SD of 9, with 80% power and 5% two-sided alpha. However, a clustering effect may be expected to occur in the intervention arm due to the intervention being delivered in groups. Based on an average treatment group size of five evaluable participants and an inter-cluster correlation of 0.1 in the intervention group, an optimal allocation ratio of 6:5 in favour of the intervention group, a total of 336 evaluable patients would provide 80% power to detect such a difference. A total of 400 participants were to be randomized (216 to intervention and 184 to usual care) to allow for non-collection of primary outcome data in 15% of participants.

The planned analyses were summarized in the Statistical Analysis Plan and Health Economic Analysis, which were finalized prior to database lock and release of the treatment allocation codes for analysis. All analyses were conducted using Stata/SE 14.1/15.1.

The analysis was a modified intention-to-treat, that is, analysis according to randomized group regardless of adherence to allocation and including only participants who provided outcome data at follow-up. The difference in mean outcome scores between the two groups at each time point was estimated using a multilevel linear model with site, multiple sclerosis type, gender and baseline score as covariates. Individuals allocated to usual care had no contact with each other, and outcomes in this group were therefore assumed to be independent. However, participants allocated to cognitive rehabilitation received sessions together in groups. Therefore, a fully heteroscedastic model estimated group-level residual variance in the intervention group and also permitted individual-level residual variance to differ between groups. Assumptions for the multilevel linear model were checked using diagnostic plots. Missing baseline scores were imputed for the analysis using the mean score at each site.

The primary health economic outcome consisted of a cost-utility analysis at 12 months. Utility was estimated from EQ-5D-5L responses cross-walked to the 3L value set for England consistent with the guidance from the National Institute for Health and Care Excellence.²¹ Cost-utility and cost-effectiveness analyses were undertaken to estimate the incremental cost per QALY gained and incrementally cost per improvement in Multiple Sclerosis Impact Scale Psychological subscale score based on the primary clinical endpoint. Results of the comparative analysis of incremental costs and effects were summarized as incremental cost-effectiveness ratios.

The study was overseen by an independent Trial Steering Committee and Data Monitoring Committee.

Results

Of the 449 participants randomized, 245 were allocated to cognitive rehabilitation and 204 to usual care (see CONSORT diagram, Figure 1).

The groups appeared well-matched on baseline characteristics (Table 1) and on baseline scores on questionnaire measures and cognitive tests (Table 2).

Of the 245 allocated to cognitive rehabilitation, 208 (85%) attended at least three sessions, the minimum number considered likely to effect a change. The mean attendance was 7.7 sessions (SD = 3.5, range = 0–10). Based on the Use of Health and Social Services questionnaire and feedback interviews, participants in the usual care group received no cognitive rehabilitation.

Of the 449 participants, 214 (87%) in the intervention group and 173 (85%) in the control group were included in the primary analysis (see Figure 1).

There was no evidence of any clinically important difference between the groups on the primary outcome, the Multiple Sclerosis Impact Scale Psychological subscale at 12 months (Table 3). Analysis of secondary outcomes showed there was evidence of a small difference on the Multiple Sclerosis Impact Scale Psychological subscale at 6 months favouring cognitive rehabilitation. Differences favouring cognitive rehabilitation were also found on the Everyday Memory Questionnaire-participant and relative versions, and the

General Health Questionnaire 30, at both 6 and 12 months (Table 3). There were no differences on the Multiple Sclerosis Impact Scale Physical subscale, cognitive tests, fatigue or Modified Carer Strain Index. Employment status was no different between the groups. The level of disability on the Guys Neurological Disability Scale and number of relapses were similar in the two groups, indicating that results were not due to changes in the physical progression of multiple sclerosis.

No safety concerns were raised and no deaths reported. The cost of delivering the cognitive rehabilitation was estimated at £209 per participant, with 77% of the total cost attributable to the Assistant Psychologist delivering sessions. Mean total costs associated with cognitive rehabilitation of £5885 ($n=208$) were over £800 lower than those of usual care £6574 ($n=170$), but there was no evidence of a difference ($P=0.27$). Despite small QALY gains at 12 months for both groups, there was no evidence of a difference between groups ($P=0.2$). The use of multiple imputation to address missing data for both costs and outcomes produced similar results with no evidence of a cost or QALY difference between groups (see Table 4).

Lower scores on the Multiple Sclerosis Impact Scale Psychological subscale represent less psychological impact of multiple sclerosis on quality of life; therefore, negative incremental differences favour the intervention. Positive incremental QALY differences favour the intervention.

The cost-effectiveness plane for the EQ-5D (Figure 2) shows a distribution of estimates centred in the bottom right hand quadrant consistent with cognitive rehabilitation dominating usual care.

The cost-effectiveness acceptability curve (Figure 3) shows a high probability of the intervention being cost-effective at willingness-to-pay thresholds between £0 and £100,000. At a willingness-to-pay threshold of £30,000 per QALY gained, cognitive rehabilitation has a 97% probability of being cost-effective.

Discussion

This cognitive rehabilitation programme provided in addition to usual care did not reduce the psychological impact of multiple sclerosis on quality of life at

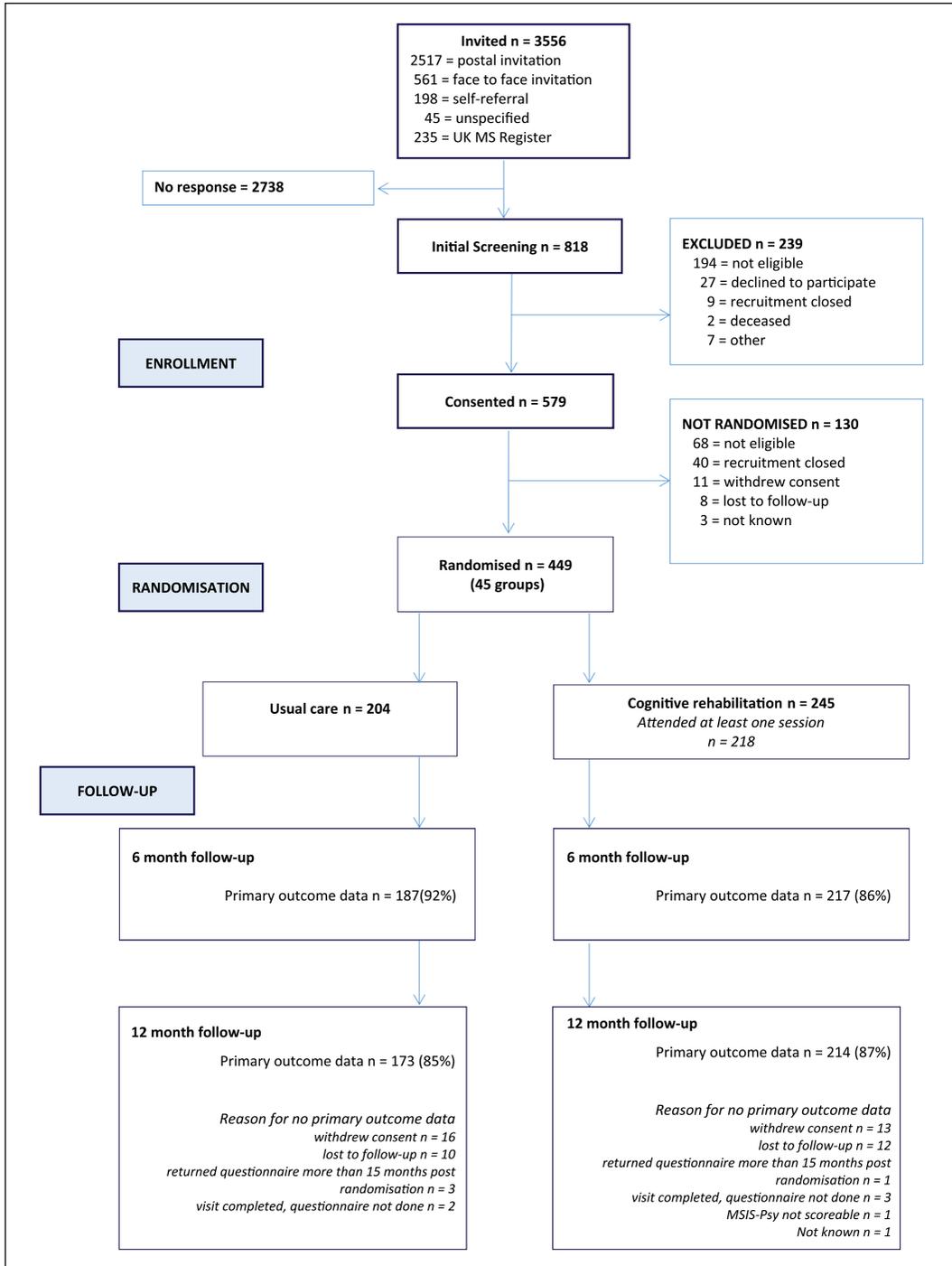


Figure 1. Participant flow.

Table 1. Baseline characteristics of participants.

Demographic and clinical characteristics		Cognitive rehabilitation (n = 245)		Usual care (n = 204)	
		Mean	SD	Mean	SD
Age (years)		49.9	9.8	48.9	10.0
Years of education		14.2	3.4	13.9	2.9
Years since diagnosis		12.1	8.0	11.1	8.7
		n	%	n	%
Gender	Men	67	27	56	27
	Women	178	73	148	73
Ethnicity	White	237	97	195	96
	Non-White	8	3	9	4
Marital status	Single/divorced/widowed	81	33	66	32
	Married/with partner	164	67	138	68
Living arrangements	Alone	49	20	38	19
	With others	196	80	166	81
Employment status	Not employed	163	67	134	65
	Employed or in education	82	33	69	34
Type of multiple sclerosis	Relapsing–remitting	159	65	132	65
	Primary progressive	22	9	24	12
	Secondary progressive	64	26	48	24

Table 2. Baseline scores on Questionnaires and cognitive tests.

Measure		Cognitive rehabilitation			Usual care		
		n	Mean	SD	n	Mean	SD
Multiple Sclerosis Neuropsychological Questionnaire		245	38.9	7.1	204	39.0	7.4
Multiple Sclerosis Impact Scale	Psychological	233	23.3	5.8	197	24.7	6.0
	Physical	232	52.0	13.6	197	53.4	13.1
General Health Questionnaire-30		230	36.5	14.2	197	39.7	15.8
Everyday Memory Questionnaire	Participant	229	45.0	22.8	194	47.1	23.2
	Relative	213	34.7	23.4	185	38.2	25.9
Fatigue Severity Scale		230	1.4	1.4	197	1.3	1.3
Guys Neurological Disability Scale		245	19.9	7.1	204	20.0	6.7
EQ-5D-5L	Visual analogue	245	59.9	21.2	203	59.6	20.3
	Selective reminding total	245	40.6	11.0	204	40.2	10.5
Brief Repeatable Battery	Selective reminding delay	245	5.8	2.8	204	5.7	2.8
	10/36 Spatial recall total	245	18.1	4.5	204	18.3	4.9
	10/36 Spatial recall delay	245	6.0	2.2	204	6.3	2.1
	Symbol digit	244	36.3	11.5	204	37.8	12.1
	PASAT–easy	239	31.6	16.2	199	31.3	16.4
	PASAT–hard	239	17.3	16.5	199	15.9	15.8
	Word fluency	244	24.8	8.8	203	25.1	8.9
Doors and people	Overall age scaled score	245	7.0	3.7	203	7.0	3.9
Trail making	B–A	244	71.7	41.0	200	69.6	41.4

EQ-5D-5L, European Quality-of-Life five-level; PASAT, Paced Auditory Serial Addition Test.

Table 3. Comparison of primary and secondary outcomes at 6- and 12-month follow-up.

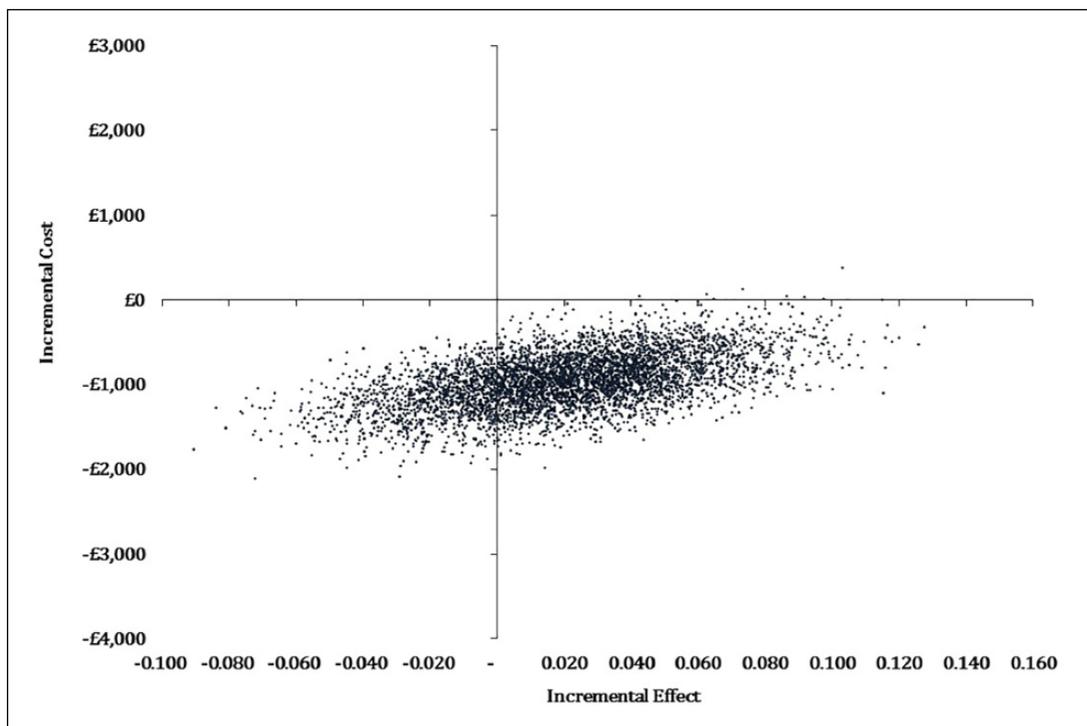
	Time point (months)	Cognitive rehabilitation			Usual care			Adjusted difference		
		n	Mean	SD	n	Mean	SD	Mean	95% CI	P value
Primary outcome										
MSIS-psychological	12	214	22.2	6.1	173	23.4	6.0	-0.6	-1.5 to 0.3	0.20
Secondary outcomes										
MSIS-psychological	6	217	22.3	6.2	187	24.1	5.9	-0.9	-1.7 to -0.1	0.03
MSIS-physical	6	215	51.4	13.3	187	53.0	3.9	-0.6	-2.2 to 0.9	
	12	214	51.8	14.0	173	52.5	13.6	-0.1	-1.8 to 1.5	
Everyday Memory Questionnaire-participant	6	214	37.6	23.4	181	44.5	23.5	-5.3	-8.7 to -1.9	
	12	210	37.9	22.9	168	43.1	24.0	-4.4	-7.8 to -0.9	
Everyday Memory Questionnaire-relative	6	184	31.3	22.7	152	38.6	25.7	-5.4	-9.1 to -1.7	
	12	164	30.5	23.3	142	38.5	26.4	-5.5	-9.6 to -1.5	
General Health Questionnaire-30	6	212	32.9	15.1	183	37.8	14.8	-3.4	-5.9 to -0.8	
	12	209	33.9	16.1	167	38.3	16.2	-3.4	-6.2 to -0.6	
Fatigue Severity Scale	6	214	1.1	1.4	185	1.1	1.4	-0.1	-0.3 to 0.2	
	12	210	1.0	1.4	168	1.2	1.4	-0.3	-0.5 to 0.0	
EQ-5D Visual Analogue	6	224	61.7	19.5	187	59.9	20.2	2.6	-0.9 to 6.0	
	12	209	61.6	19.3	173	59.7	20.0	2.6	-0.9 to 6.0	
Brief Repeatable Battery										
Selective reminding total	6	220	45.6	10.5	182	43.5	10.4	1.6	0.1 to 3.0	
	12	206	47.5	10.9	170	46.5	11.3	0.6	-0.9 to 2.1	
Selective reminding delay	6	220	6.7	2.9	182	6.5	2.9	0.2	-0.2 to 0.6	
	12	206	7.5	2.8	170	7.1	2.9	0.4	0.1 to 0.8	
10/36 Total	6	217	19.1	5.3	182	19.8	5.4	-0.6	-1.5 to 0.3	
	12	206	20.1	4.9	170	20.4	5.4	-0.1	-1.0 to 0.8	
10/36 Delay	6	217	6.6	2.3	182	6.6	2.3	0.0	-0.4 to 0.4	
	12	206	6.8	2.2	170	7.0	2.3	-0.1	-0.5 to 0.2	
Symbol digit	6	220	41.4	12.1	181	40.7	12.7	1.3	-0.6 to 3.2	
	12	205	39.9	11.9	170	39.9	12.8	0.4	-1.7 to 2.5	
Paced serial addition easy	6	217	36.6	16.1	178	35.7	17.6	0.0	-2.4 to 2.5	
	12	205	36.4	17.8	169	36.5	17.7	-0.6	-3.1 to 1.9	
Paced serial addition hard	6	217	20.7	17.5	178	19.3	17.7	-0.3	-2.9 to 2.2	
	12	205	18.5	19.2	169	19.2	18.9	-1.9	-4.8 to 1.0	
Word fluency	6	219	27.4	9.4	182	27.2	9.3	0.0	-1.3 to 1.3	
	12	206	28.0	10.3	169	28.3	10.2	-0.2	-1.5 to 1.2	
Doors and people (overall age scaled score)	6	221	9.5	4.2	181	9.1	4.4	0.4	-0.1 to 0.9	
	12	206	10.5	4.1	168	9.9	4.4	0.6	0.0 to 1.1	
Trail making (B-A)	6	218	63.0	39.1	179	62.3	38.3	-0.3	-6.8 to 6.2	
	12	205	61.3	39.7	165	63.0	40.3	-3.2	-10.0 to 3.6	
Carer strain index	6	173	5.9	5.6	154	6.8	6.2	-0.9	-2.2 to 0.4	
	12	159	5.8	5.2	141	6.2	6.0	-0.4	-1.6 to 0.8	
Any employment				%			%	Odds ratio	95% CI	
	6		62/224	28	57/187	30	0.88	0.55 to 1.39		
	12		60/209	29	50/173	29	0.99	0.60 to 1.63		

CI, confidence interval; MSIS, Multiple Sclerosis Impact Scale.

Table 4. Cost- and quality-adjusted life year outcomes at 12-month follow-up.

	Usual care (n = 170)		Cognitive rehabilitation (n = 208)		Adjusted difference		Cost effectiveness plane
	Mean	SD	Mean	SD	Mean	95% CI	
Costs	6574	9188	5885	5641	-808	-2248 to 632	
EQ-5D quality- adjusted life years	0.57	0.27	0.60	0.25	0.01	-0.03 to 0.05	SE quadrant intervention dominant
MS Impact Scale Psychological	23.4	6.0	22.2	6.1	-0.6	-1.5 to 0.3	SE quadrant intervention dominant

CI, confidence interval; MS, multiple sclerosis; SE, south-east.

**Figure 2.** Cost-effectiveness plane for EQ-5D-5L QALYs at 12 months.

12 months compared to usual care alone, but there was a small reduction in the psychological impact of multiple sclerosis at 6 months. Thus, there was some evidence to suggest that cognitive rehabilitation improved quality of life in the short term, but the effects were not maintained over time. There were differences between groups in the frequency of subjective complaints of cognitive problems from both

people with multiple sclerosis and their relatives and mood at both the 6- and 12-month follow-ups favouring the cognitive rehabilitation group.

Strengths of the study included a large sample size (with previous studies of cognitive rehabilitation having a mean of 42 participants)² and good attendance at sessions, so most people received most of the intervention. The attendance rate was

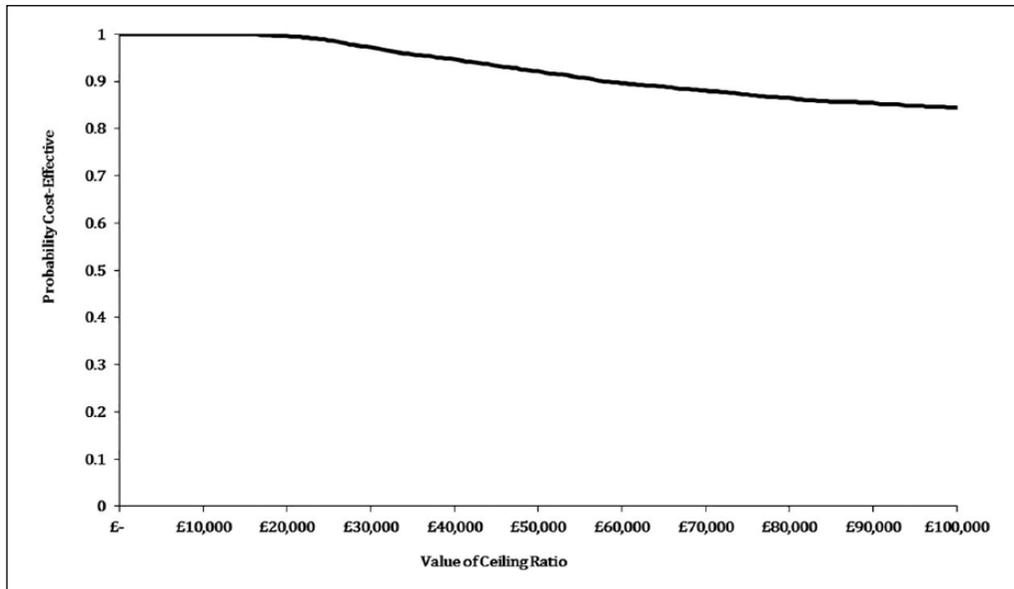


Figure 3. Cost-effectiveness acceptability curve for EQ-5D-5L QALYs at 12 months.

consistent with the pilot study;⁶ however, many studies do not report attendance rates,²² so direct comparisons of attendance rates across trials are limited. The reasons for non-attendance reflect aspects of daily life unrelated to cognitive problems, such as illness and holidays, rather than not wanting to continue in the group.

There are, however, some limitations to the study. The lack of information on demographic characteristics of those who did not wish to take part limits the ability to determine the proportion of people who would be eligible for the treatment if it were routinely available. As a pragmatic trial, the inclusion criteria were intentionally broad to involve all those who might be treated in clinical practice, thereby increasing generalizability of the findings. However, almost half of those excluded was due to scoring too low on the Multiple Sclerosis Neuropsychological Screening Questionnaire, yet they believed they had cognitive difficulties. In the pilot study,⁶ participants were recruited if they reported cognitive problems in daily life and no standardized assessment was used. The Multiple Sclerosis Neuropsychological Screening Questionnaire was used to provide a

more replicable criterion. However, the cut-off of >27 was based on the original validation study¹¹ and lower cut-offs have been recommended subsequently.^{23–25} Therefore, the sample included those with relatively severe cognitive problems in daily life, and these people may benefit less from the intervention.²⁶

The primary outcome was the Multiple Sclerosis Impact Scale Psychological subscale, which was developed specifically for people with multiple sclerosis, and includes items on mood, coping and cognition; it has good psychometric properties and has been shown to be sensitive to the effects of rehabilitation. However, even on the Psychological subscale, some items are unlikely to be directly influenced by cognitive rehabilitation (such as ‘feeling unwell’ or ‘problems sleeping’). Impact of multiple sclerosis and quality of life are multidomain constructs, and changing the impact of multiple sclerosis on quality of life, although desirable, may be unrealistic for interventions that focus on specific symptoms of multiple sclerosis. The research funder’s commissioning brief indicated that quality of life in the longer term was an important outcome, and therefore, the Multiple Sclerosis

Impact Scale Psychological subscale at 12-month follow-up was used.

These findings are consistent with previous cognitive rehabilitation research in people with multiple sclerosis,^{27,28} in that they show benefits of cognitive rehabilitation that focusses on teaching strategies to cope with cognitive impairments in daily life on measures of memory problems in daily life. However, comparison with the ReMemBrIn trial,²⁶ which evaluated the same intervention in people with traumatic brain injury, suggested that those with multiple sclerosis responded better than those with traumatic brain injury. One possible reason is that usual care for people with traumatic brain injury in the United Kingdom often includes cognitive rehabilitation, whereas it does not for people with multiple sclerosis.

The finding of a beneficial effect on mood supports our pilot trial⁶ and the multiple sclerosis subgroup analysis of that trial,²⁹ both of which used a similar treatment approach, and with a previous study of group treatment.²⁷ A strong relationship has previously been documented³⁰ between subjective cognitive problems and mood in people with multiple sclerosis. The beneficial effect on mood could therefore be partly attributable to the social contact afforded by attending sessions rather than the content of the intervention. However, it seems more likely that the change in mood was in response to changes in everyday memory because relatives' reports of the frequency of everyday memory problems also showed a difference between groups, favouring the intervention group.

The results indicated that the intervention had no effect on cognitive impairment, as assessed on cognitive tests. In most studies which show changes in cognitive function, the intervention comprises direct retraining of cognitive skills. The focus of the intervention in the cognitive rehabilitation for attention and memory in people with multiple sclerosis (CRAMMS) trial was on learning to cope with cognitive problems, and therefore, cognitive abilities would not necessarily be expected to change. There was also no evidence to suggest that the intervention exacerbated fatigue-related problems, which is positive and consistent with previous trials of cognitive rehabilitation.²

The incremental cost-effectiveness analysis indicates that cognitive rehabilitation was less costly and more effective than usual care, suggesting dominance of the intervention. However, differences in both costs and effects were small with no evidence of a difference between groups. The key cost drivers were medications and social services; however, for each component of the Use of Health and Social Services Questionnaire, outliers had a substantial impact on the mean value, with a few high-cost users increasing the average cost resulting in high SDs.

Overall, the trial showed no effect of cognitive rehabilitation on the psychological impact of multiple sclerosis on quality of life in the long term, but there were modest benefits in the short term and a reduction in self-reported cognitive problems in daily life and improved mood. Future research should investigate whether there are subgroups who benefit from this intervention and ways in which the effects of cognitive rehabilitation can be maintained over time, such as including booster sessions or additional on-line support. In addition, evaluating the intervention in a less cognitively impaired sample would identify whether earlier intervention would be beneficial. Incorporating this trial in Cochrane review meta-analyses may provide more robust and reliable data to inform a future model-based economic analysis.

Clinical messages

- We found no long-term effect of this cognitive rehabilitation programme on the impact of multiple sclerosis on quality of life.
- Cognitive rehabilitation improved memory problems in daily life and mood.

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Author contributions

N.B.L. was the chief investigator and coauthored the final report. L.E.B. analysed the clinical effectiveness data and prepared the results for publication. C.S.C. contributed to the development of the grant application and trial protocol and contributed important intellectual content to the report. F.D. contributed to preparation of the final report. A.E.R.D. contributed to the development of the grant application and trial protocol and contributed important intellectual content to the report. D.F. oversaw the health economics analysis and contributed important intellectual content to the report. S.H. analysed the health economics data and contributed important intellectual content to the report. A.A.M. contributed to the development of the grant application and trial protocol, oversaw the clinical effectiveness analysis and contributed important intellectual content to the report. R.d.N. was the co-chief investigator and coauthored the final report.

Declaration of conflicting interests

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Supplemental material

Supplemental material for this article is available on-line.

References

1. Amato MP, Langdon D, Montalban X, et al. Treatment of cognitive impairment in multiple sclerosis: position paper. *J Neurol* 2013; 260(6): 1452–1468.
2. das Nair R, Martin KJ and Lincoln NB. Memory rehabilitation for people with multiple sclerosis. *Cochrane Database Syst Rev* 2016; 3: CD008754.
3. Rosti-Otajarvi EM and Hamalainen PI. Neuropsychological rehabilitation for multiple sclerosis. *Cochrane Database Syst Rev* 2014; 10: CD009131.
4. Mitolo M, Venneri A, Wilkinson ID, et al. Cognitive rehabilitation in multiple sclerosis: a systematic review. *J Neurol Sci* 2015; 354: 1–9.
5. das Nair R and Lincoln NB. Evaluation of rehabilitation of memory in neurological disabilities (ReMiND): a randomised controlled trial. *Clin Rehabil* 2012; 26: 894–903.
6. Carr SE, das Nair R, Schwartz AF, et al. Group memory rehabilitation for people with multiple sclerosis: a feasibility randomized controlled trial. *Clin Rehabil* 2014; 28(6): 552–561.
7. Lincoln NB, Bradshaw LE, Constantinescu CS, et al. Cognitive rehabilitation for attention and memory in people with multiple sclerosis: a randomised controlled trial (CRAMMS). *Health Technol Assess*. In press.
8. Lincoln NB, das Nair R, Bradshaw L, et al. Cognitive rehabilitation for attention and memory in people with multiple sclerosis: study protocol for a randomised controlled trial (CRAMMS). *Trials* 2015; 16: 556.

9. Benedict RHB, Munschauer F, Linn R, et al. Screening for multiple sclerosis cognitive impairment using a self-administered 15-item questionnaire. *Mult Scler* 2003; 9(1): 95–101.
10. Rao SM and the Cognitive Function Study Group of the National Multiple Sclerosis Society. *A manual for the brief repeatable battery of neuropsychological tests in multiple sclerosis*. Milwaukee, WI: Medical College of Wisconsin, 1990.
11. Sepulcre J, Vanotti S, Hernandez R, et al. Cognitive impairment in patients with multiple sclerosis using the Brief Repeatable Battery-Neuropsychology test. *Mult Scler* 2006; 12(2): 187–195.
12. Rossier P and Wade DT. The Guy's Neurological Disability Scale in patients with multiple sclerosis: a clinical evaluation of its reliability and validity. *Clin Rehabil* 2002; 16(1): 75–95.
13. Hobart J, Lamping D, Fitzpatrick R, et al. The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. *Brain* 2001; 124(pt 5): 962–973.
14. Goldberg RJ and Williams PA. *A user's guide to the General Health Questionnaire*. Windsor: NFER-Nelson, 1988.
15. Sunderland A, Harris JE and Baddeley AD. Do laboratory tests predict everyday memory? A neuropsychological study. *J Verbal Learning Verbal Behav* 1983; 22: 341–357.
16. Mills R, Young C, Nicholas R, et al. Rasch analysis of the Fatigue Severity Scale in multiple sclerosis. *Mult Scler* 2009; 15: 81–87.
17. Baddeley AD, Emslie H and Nimmo-Smith I. 1994 *Doors and people: a test of visual and verbal recall and recognition*. Bury St Edmunds: Thames Valley Test Company.
18. Delis DC, Kaplan E and Kramer JH. *Delis-Kaplan executive function system: examiners manual*. San Antonio, TX: Psychological Corporation, 2001.
19. EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. *Health Policy* 1990; 16(3): 199–208.
20. Thornton M and Travis SS. Analysis of the reliability of the modified caregiver strain index. *J Gerontol B Psychol Sci Soc Sci* 2003; 58(2): S127–S132.
21. National Institute for Health and Care Excellence (NICE). Position statement on the use of the EQ-5D-5L valuation set, https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/eq5d5l_nice_position_statement.pdf (accessed August 2017).
22. Mhizha-Murira JR, Drummond A, Klein OA, et al. Reporting interventions in trials evaluating cognitive rehabilitation in people with multiple sclerosis: a systematic review. *Clin Rehabil* 2018; 32(2): 243–254.
23. Benedict RH, Cox D, Thompson LL, et al. Reliable screening for neuropsychological impairment in multiple sclerosis. *Mult Scler* 2004; 10(6): 675–678.
24. O'Brien A, Gaudino-Goering E, Shawaryn M, et al. Relationship of the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) to functional, emotional, and neuropsychological outcomes. *Arch Clin Neuropsychol* 2007; 22(8): 933–948.
25. Nauta IM, Balk LJ, Sonder JM, et al. The clinical value of the patient-reported multiple sclerosis neuropsychological screening questionnaire. *Mult Scler* 2019; 25: 1543–1546.
26. das Nair R, Bradshaw LE, Carpenter H, et al. A group memory rehabilitation programme for people with traumatic brain injuries: the ReMemBrIn RCT. *Health Technol Assess*, 2019; 23: 16.
27. Hanssen KT, Beiske AG, Landrø NI, et al. Cognitive rehabilitation in multiple sclerosis: a randomized controlled trial. *Acta Neurol Scand* 2016; 133: 30–40.
28. Mäntynen A, Rosti-Otajärvi E, Koivisto K, et al. Neuropsychological rehabilitation does not improve cognitive performance but reduces perceived cognitive deficits in patients with multiple sclerosis: a randomised, controlled, multi-centre trial. *Mult Scler* 2014; 20: 99–107.
29. Martin KJ, Lincoln NB and Nair RD. Group-based memory rehabilitation for people with multiple sclerosis: Subgroup analysis of the ReMiND trial. *Int J Ther Rehabil* 2014; 21: 590–596.
30. Rosti-Otajärvi E, Ruutiainen J, Huhtala H, et al. Relationship between subjective and objective cognitive performance in multiple sclerosis. *Acta Neurol Scand* 2014; 130(5): 319–327.